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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/229,283	01/13/1999	DAVID E. FISCHER	48012	7211

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EXAMINER

UNGAR, SUSAN NMN

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 08/19/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/229,283

Applicant(s)
Fischer

Examiner
Ungar

Art Unit
1642



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jun 18, 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above, claim(s) 5-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 13, and 14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other: _____

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1. The Amendment filed June 18, 2003 (Paper No. 14) in response to the Office Action of January 17, 2003 (Paper No. 12) is acknowledged and has been entered. Previously pending claims 1, 3 and 4 have been amended and new claims 13-14 have been added. Claims 1-4 and 13-14 are currently under consideration.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. The following rejections are maintained:

Claim Rejections - 35 USC § 112

4. Claims 1-4 remain rejected under 35 USC 112, first paragraph and newly added claims 13-14 are rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 15, Section 8, pages 4-7.

Applicant argues (a) that it is easy to distinguish the morphology of normal and malignant cells because tumor cells are different than normal cells because they do not exhibit normal cell contact inhibition and thus will grow on top of each other, piling up and/or growing as a mass. Further, claim 1 requires the expression of Mi in malignant cells and it is extremely unlikely that osteoclasts or mast cells or melanocytes would be present in most samples, (b) specifically Mi is useful for distinguishing melanoma from other possible cancers, not for distinguishing cancerous cells from healthy cells and Applicant specifically points to page 2 of the specification.

The arguments have been considered but have not been found persuasive because (a') Applicant is arguing limitations not recited in the claims as currently constituted, the claims are not limited to assays wherein the morphology of the cells

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is visible or diagnosing melanoma in advanced tumors wherein the tumor cells are growing on top of each other, piling up and/or growing as a mass. Further, the claims as currently constituted do not recite the method wherein the assayed tissue is compared to normal controls and the issue was raised because it is clear from the teaching of the specification that a preferred method was a method in which confounding cells are not included in the sample. In addition, although Applicant states that it is extremely unlikely that osteoclasts or mast cells or melanocytes would be present in most samples, it is clear that the invention is drawn not only to primary tumors but also to metastatic tumors and it would be expected that a subset of metastatic tumors would be found among those cells. Finally, although, a review of Figure 6 reveals differential staining of melanoma in situ as compared to normal control, not only malignant cells but also benign nevus and dysplastic nevus cells, which are not malignant, all show staining in the melanocytic component of these lesions, (b') Applicant is attempting to broaden the teachings of the specification. A review of page 2 clearly reveals that the teaching is drawn to determining the origin of metastatic tissue, not distinguishing melanoma from other possible tumors. It is noted, for Applicant's convenience, that amendment of claim 1 to include a limitation drawn to distinguishing melanoma from other possible tumors would result in a rejection of the claims under the new matter provision of 35 USC112, first paragraph. Further, if such an amendment were made a rejection based on the disclosure at p. 11, lines 1-5 of the specification would be made. The specification clearly reports that two nonmelanoma tumors were found to stain positive for Mi. Clearly these cells are malignant, clearly they stain positive for Mi and therefore

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they meet the limitations of the claims and would be diagnosed as melanoma using the instantly claimed method. However, just as clearly, they are nonmelanoma tumors. The arguments have been considered but have not been found persuasive and the rejection is maintained.

5. Claims 1-4 remain rejected under 35 USC 112, first paragraph and newly added claims 13-14 are rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 15, Section 9, pages 7-9.

Applicant argues that the ability of an Mi probe to discriminate between the isoforms will not effect its utility for diagnosing melanoma for the reasons set forth above. What is important for the present method is the positive staining of tumor tissue with an Mi probe wherein the presence of such Mi in the malignant cell indicates a positive diagnosis of melanoma. The broad teaching of the specification indicates that expression of Mi in cancer cells is diagnostic of melanoma and this has been repeatedly confirmed in practice. The argument has been considered but has not been found persuasive because the issue raised is not drawn to whether or not an Mi probe can discriminate between the isoforms but rather that only the M isoform is known to be associated with melanoma. The claims as written read on the diagnosis of melanoma with assay for the broadly claimed microphthalmia transcription factor, which includes both the A and H forms. Applicant has not taught how to use the broadly claimed method for diagnosing melanoma with the broadly claimed microphthalmia transcription factors. The arguments have been considered but have not been found persuasive and the rejection is maintained. It is noted that Applicant has not addressed the issue drawn to the specificity of the

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probe, that is drawn to the probe that binds to the amino terminal Taq-Sac fragment of human MITF which is specific for human Mi but not for related proteins.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a method for diagnosing melanoma with a probe that detects the presence of mRNA expressing Mi in malignant cells. The specification teaches that mRNA can be detected using Northern blotting as well as in situ hybridization on a thin section of biopsy (p. 9, line 25 to p. 10, line 3). One cannot extrapolate the teaching of the specification to the enablement of the claims because although it appears that protein is differentially expressed in melanoma cells when compared with normal cells, given the teaching of the specification that using the monoclonal antibody to Mi resulted in strong nuclear staining within nevi, dysplastic nevi, melanoma in situ and in melanomas, no such finding has been disclosed or demonstrated for mRNA. In particular, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For instance, Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147)

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teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Carrere et al (Gut, 1999, vol. 44, pp. 55-551) teach an absence of correlation between protein and mRNA levels for the Reg protein. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-translational level. These references serve to demonstrate that levels of polypeptide expression cannot be relied upon to anticipate levels of polynucleotide expression. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific protein expressed by a cell will be paralleled at the mRNA level due to complex homeostatic factors controlling translation and post-translational. Given the above, it cannot be predicted that the mere presence of mRNA expression of Mi could be used for the diagnosis of melanoma or that the presence of mRNA expression of Mi

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could be used to differentiate between normal, nevi, dysplastic nevi and melanoma cells. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to use the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. All other objections and rejections recited in Paper No. 12 are withdrawn.
8. No claims allowed.
9. Applicant's amendment necessitated the new grounds of rejection.

Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.


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10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.


Susan Ungar
Primary Patent Examiner
August 14, 2003